CLOZAPINE TDM: A COMPARISON of LC/MS/MS, POINT of CARE and IMMUNOASSAY

Christian Cooper[1], Kayleigh Davis[1], Matthew Atkins[2], David Taylor[2], Philip McGuire[3], Irina Baburina[4], Salvatore Salamone[4], Dave Berry[1]

[1]Viapath Toxicology,Kings College Hospital, [2]Maudsley Hospital , [3]Institute of Psychiatry, King's College, [4]Saladax Biomedical, Inc.

Background

The value of measuring clozapine plasma levels to obtain optimum clinical response, avoid drug-related CNS toxicity and assess patient adherence to treatment has been widely reported in many studies which have led to practice guidelines and expert consensus recommendations. Clozapine TDM is normally undertaken on venipuncture blood specimens that are sent to a specialist laboratory for drug determination. Transportation and analysis inevitably takes several days. This study has two aims:- a) to validate the three title methods against a blinded clozapine spiked sample set with performance between each method compared; b) compare, in real patient samples, plasma clozapine concentrations from venipuncture blood measured by LC/MS/MS with capillary blood levels collected at the same time and determined using the MyCare Insite point of care device operated by the reviewing clinician; in addition, to compare plasma concentration obtained by MyCare laboratory based Immunoassay (IA).

Methods

Initially a spiked plasma sample set was blinded by Saladax and sent to Viapath for analysis by their LC/MS/MS method. The same sample set was analysed by the SBI immunoassay run on an AU480 and the set was also tested with the MyCare Insite PoCT.

304 samples were collected for method comparison during routine patient visits at two sites of the South London and Maudsley NHS Foundation Trust. Capillary whole blood samples were tested immediately by two operators using four MyCare Insite analysers. An EDTA venous plasma sample was simultaneously drawn for laboratory analysis by the LC-MS/MS method at Viapath Toxicology. Residual plasma was frozen at -20C and batch shipped to Saladax for analysis using the SBI immunoassay.

Results

Tables below summarise regression statistics for the LC/MS/MS method versus the spiked values in the blinded sample set together with a comparisons of both the SBI immunoassay and MyCare Insite vs LC/MS/MS for the spiked samples.

Viapath LC/MS/MS vs Spiked Plasma values

	Deming	Passing-Bablok	Reg. Linear Regression
Slope (95% CI)	0.965 (0.954 to 0.9770	0.972 (0.957 to 0.987)	0.965 (0.953 to 0.977)
Intercept (95% CI)	2.2 (-9.99 to 14.4)	1.4 (-0.3 to 3.3)	2.4 (-9.7 to 14.6)
R	0.9998	0.9998	0.9998

Viapath LC/MS/MS vs SBI Immunoassay (AU480)for Spiked Plasma

	Deming	Passing-Bablok	Reg. Linear Regression
Slope (95% CI)	0.990 (0.996 to 1.014)	0.996 (0.973 to 1.025)	0.989 (0.966 to 1.013)
Intercept (95% CI)	15.5 (-2.0 to 33.0)	9.8 (0.8 to 25.4)	15.8 (-1.7 to 33.3)
R	0.9995	0.995	0.9995

Viapath LC/MS/MS vs MyCare Insite for Spiked Plasma

	Deming	Passing-Bablok	Reg. Linear Regression
Slope (95% CI)	1.022 (0.967 to 1.076)	1.040 (0.955 to 1.120)	1.019 (0.964 to 1.073)
Intercept (95% CI)	2.73 (-29.16 to 34.62)	-1.40 (-13.10 to 20.70)	3.95 (-27.92 to 35.81)
R	0.9971	0.9971	0.9971

The two tables below summarise:- a) a comparison of LC/MS/MS results vs MyCare Insite for the 309 real patient samples tested after validation of the procedure (five outliers eliminated from the analysis as were four samples with results >1.6 mg/L, the upper limit of linearity for MyCare Insite) and b) comparison of LC/MS/MS results vs SBI immunoassay for 303 samples (2 excluded because above SBI calibration range and one excluded as a high flier).

Viapath LC/MS/MS vs MyCare Insite whole blood values for 304 patient samples

	Deming	Passing-Bablok	Reg. Linear Regression
Slope (95% CI)	1.015 (0.962 to 1.068)	0.971 (0.919 to 1.025)	0.906 (0.854 to 0957)
Intercept (95% CI)	-39.8 (-66.7 to -13.0)	-21.2 (-44.6 to -2.9)	8.9 (-17.2 to 35.0)
R	0.8973	0.8973	0.8973

Viapath LC/MS/MS vs SBI immunoassay for 303 patient samples

	Deming	Passing-Bablok	Reg. Linear Regression
Slope (95% CI)	0.868 (0.830 to 0.907)	0.918 (0.878 to 0.961)	0.812 (0.774 to 0.850)
Intercept (95% CI)	37.7 (16.7 to 58.8)	22.7 (8.0 to 37.6)	64.5 (43.8 to 85.3)
R	0.9300	0.9300	0.9300

Earlier studies showed that whole-blood clozapine levels are correlated but 10-20% less than those in plasma. Our evaluation of spiked samples indicates the LC/MS/MS method is accurate, unbiased and suitable as a reference method which is also capable of providing a routine service.

Conclusions

- The Viapath LC/MS/MS clozapine method is accurate, unbiased and suitable for providing a routine laboratory based service.
- The SBI clozapine IA is accurate, unbiased and suitable for providing a routine laboratory based immunoassay service.
- MyCare Insite produced satisfactory results for the spiked trial set of plasma.
- Capillary blood samples from 304 patient tested by MyCare Insite produced a satisfactory comparison with the results produced by LC/MS/MS on matching venipuncture plasma drawn at the same time.
- 298 patient plasma samples tested by SBI IA produced a satisfactory comparison with the results produced by LC/MS/MS.
- MyCare Insite is a small, portable device for near patient testing which can measure clozapine levels in finger prick blood within 7 minutes.
- LC/MS/MS remains the gold standard, particularly if norclozapine concentrations are required.